# Chapter 7 – Neuron Physiology and Neural Signaling

## *Objectives*

Given the synopsis in this chapter, competence in each objective will be demonstrated by responding to multiple choice, matching, put-in-order, or fill-in questions, at the level of 85% or greater proficiency for each student.

A. To compare and contrast the anatomical features and functions of unipolar neurons, multipolar neurons, and glial cells.
B. To explain the role of ion channels and membrane potentials in the generation and conduction of action potentials.
C. To explain the mechanisms responsible for synaptic communication, including synaptic anatomy, neurotransmitter secretion, and neurotransmitter action.
D. To explain the mechanisms responsible for the actions of common neurotransmitters, including glutamate, GABA, glycine, acetylcholine, norepinephrine, and serotonin.
E. To explain the process and significance of integrating synaptic potentials.

# Neurons and Glial Cells

The nervous system is composed predominantly of neurons and glial cells. Classically, neurons have been associated with the functioning of the brain and spinal cord, whereas the glial cells have been associated with supporting and protecting the neurons. Recent data give glial cells a more critical role in nervous functioning, including synaptic growth and differentiation.

## Unipolar (Pseudo-unipolar) Neurons (Sensory)

Unipolar neurons are composed of a cell body with an extension of the plasma membrane, as shown in Figure 7.1. The cell bodies of unipolar neurons are typically found in the peripheral nervous system. The dendrites usually act as sensory receptors and receive signals that may be transferred to the axon (peripheral process). The axon continues into the central nervous system (central process) where it ends with synaptic bulbs.

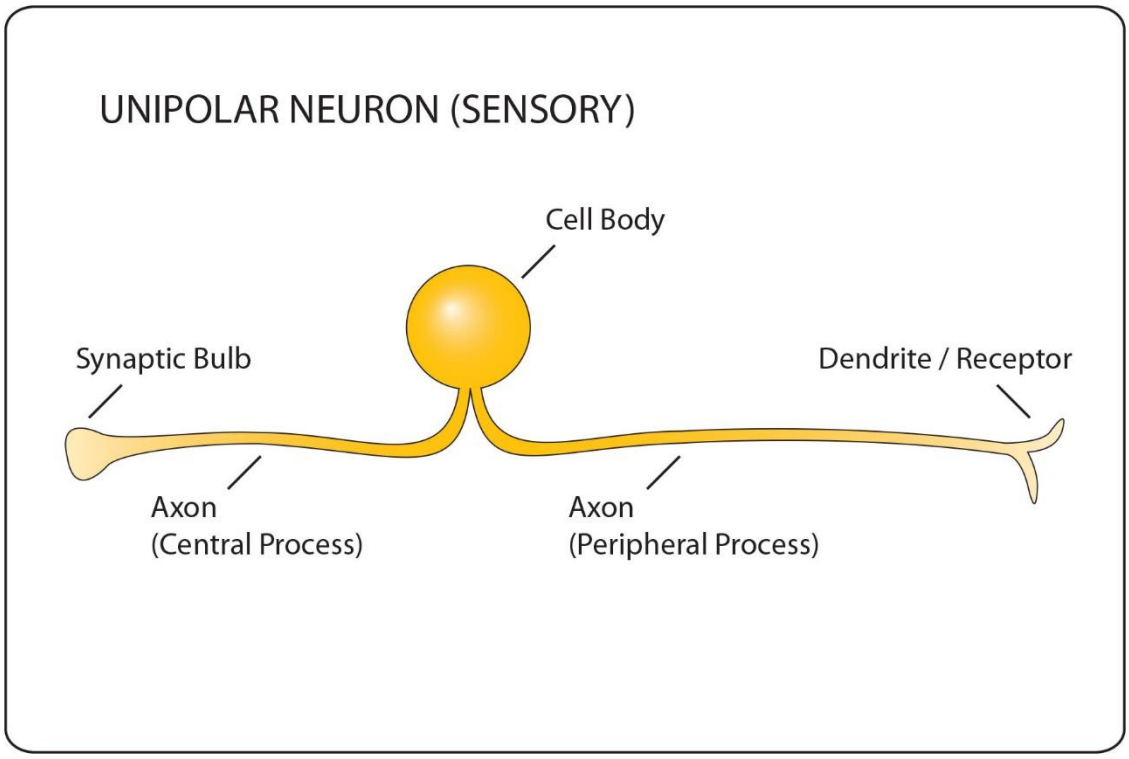


**Figure 7.1 © 2014 David G. Ward, Ph.D.**

- The **dendrites** of unipolar neurons usually function as **receptors**.
  - The dendrites contain gated channels that convert chemical or physical stimuli into changes in membrane potential (nervous signals).
  - The changes in membrane potential (graded potential) can spread to the adjacent axon and cause action potentials.

- The **axon** (**peripheral process**) functions to carry nervous signals from the dendrite.
    - The axon contains voltage gated channels which allows it to conduct action potentials from the dendrites.

- The **cell body** is usually located in the peripheral nervous system along the route of the axon.

- The axon (**central process**) continues from the cell body and carries nervous signals into the central nervous system.
    - The axon contains voltage gated channels which allows it to conduct action potentials toward the synaptic bulbs.
    - The axon often branches to form axon collaterals.

- **Synaptic bulbs** function to transfer nervous signals to adjacent neurons using chemical messengers called **neurotransmitters**.
    - Synaptic bulbs contain voltage gated channels and other receptors and convert action potentials into the release of chemical messengers

## Multipolar Neurons (Interneurons or Motor Neurons**)**

Multipolar neurons are composed of a cell body with many membrane extensions, as shown in Figure 7.2. The cell bodies of multipolar neurons are typically found in the central nervous system. The dendrites receive signals from neurons and the axons send signals to other neurons or to muscle. Interneurons connect with other neurons. Motor neurons connect with muscle cells

- The **dendrites** of multipolar neurons usually function as chemical **receptors**.
    - The dendrites contain ligand-gated channels and / or G-protein coupled receptors which respond to chemical messengers (neurotransmitters) from other neurons.
    - The dendrites convert chemical signals into changes in membrane potential.
    - The changes in membrane potential may spread to the cell body.
- The **cell body** is usually located in the central nervous system.
    - The cell body also contains ligand-gated channels and / or G-protein coupled receptors which respond to chemical messengers (neurotransmitters) from other neurons.
    - The cell body also converts chemical signals into changes in membrane potential.
- The **axon hillock** is where the axon joins the cell body.
    - The axon hillock contains voltage gated channels which respond to changes in membrane potential.
    - When the changes in membrane potential reach a threshold, the changes can cause action potentials in the axon.

- The axon is a continuation of the axon hillock.
  - The axon contains voltage gated channels which allows it to conduct action potentials toward the synaptic bulbs.
  - The axon often branch to form axon collaterals.
- **Synaptic bulbs** function to transfer nervous signals to adjacent neurons using neurotransmitters.
  - Synaptic bulbs contain voltage gated channels and other receptors and convert action potentials into the release of chemical messengers.

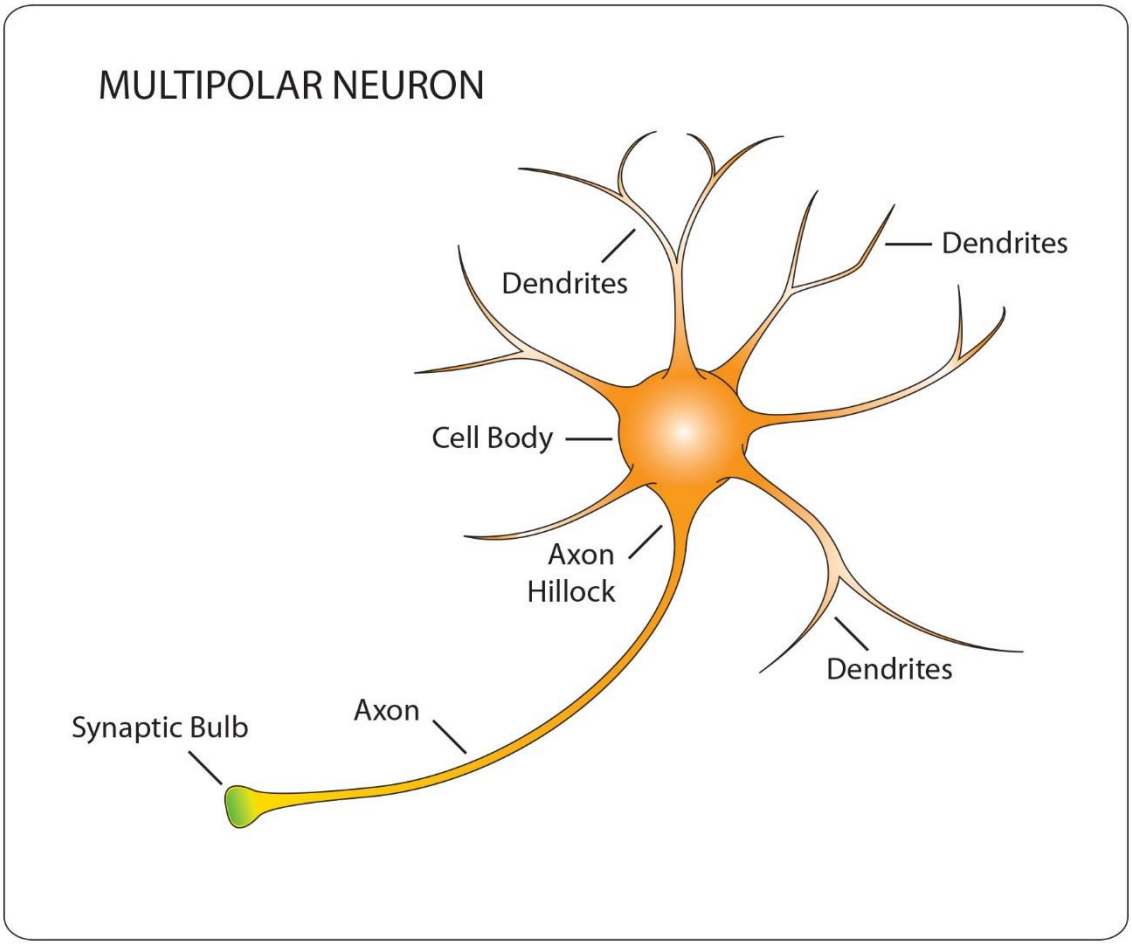


**Figure 7.2 © 2014 David G. Ward, Ph.D.**

## Glial Cells

In addition to neurons, several types of cells, called glial cells, are found in the nervous system. These include Schwann cells and oligodendrocytes, which insulate neurons in the peripheral and central nervous system; astrocytes, which protect neurons and guide

growth of synapses; and microglia, which function in immunity. Schwann cells are shown in Figure 7.3.

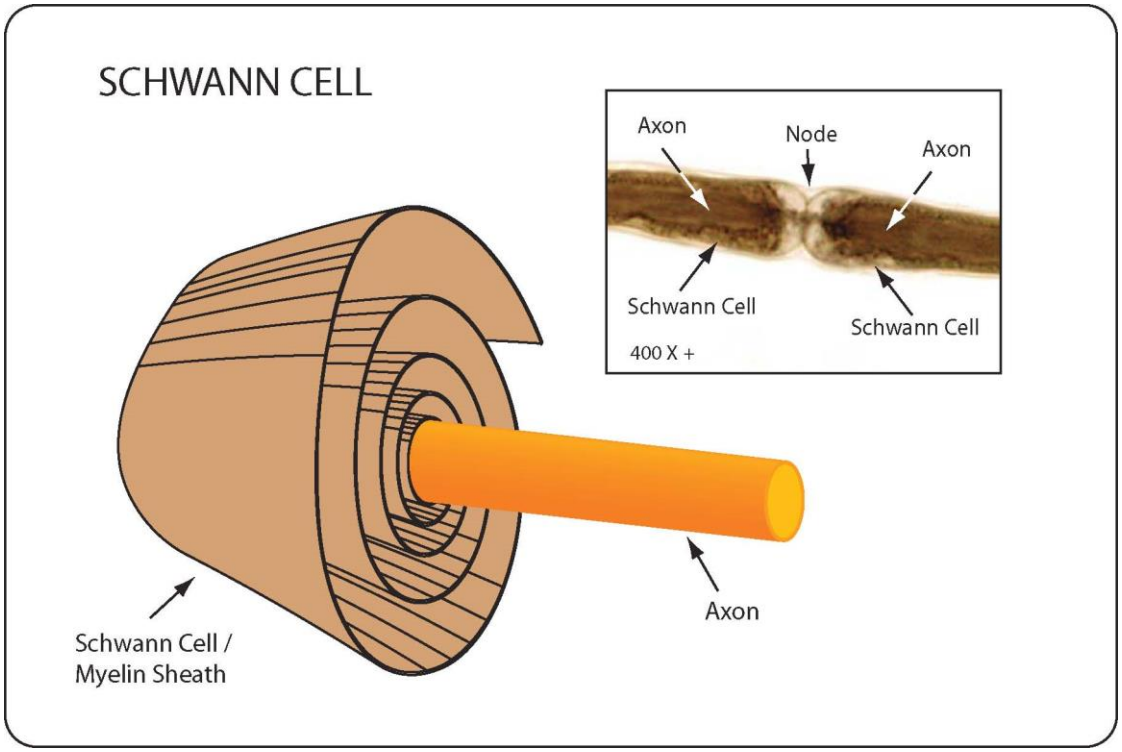


**Figure 7.3 © 2007 David G. Ward, Ph.D.**

- Schwann cells wrap around axons in the peripheral nervous system and insulate axons by forming a myelin sheath composed of the phospholipid **sphingomyelin**.
  - Gaps between adjacent Schwann cells, called **Nodes (of Ranvier)**, are prominent sites for movement of ions into and out of axons.
- Oligodendrocytes wrap around axons in the central nervous system and insulate axons also by forming a myelin sheath.
  - Oligodendrocytes have many processes that wrap around several axons.
  - Nodes are prominent sites for movement of ions into and out of axons.
- Astrocytes act as a barrier between blood vessels and neurons.
  - Astrocytes also contribute to growth and integrity of synapses, and respond to and possibly release neurotransmitters.
- Microglia function as an independent branch of the immune system in the nervous system.

# Ion Pumps, Cotransporters, Ion Channels, and Membrane Potentials

## Ion Pumps

As described in Chapter 5, cell membranes contain active transport pumps, which are transmembrane proteins that force ions through membranes from an area of lower concentration to an area of higher. Ion pumps are enzymatically active and obtain energy from the breakdown of ATP, to cause conformational changes and transport.

- The $Ca^{2+}$ pumps ($Ca^{2+}$ ATPases) force the movement of $Ca^{2+}$ out of the cytoplasm, into the extracellular fluid and/or into the smooth endoplasmic reticulum (sarcoplasmic reticulum)
  - $Ca^{2+}$ pumps are ubiquitous, especially are found in muscle cells, in synaptic bulbs, and in other secretory cells.
- The $Na^+$ / $K^+$ pumps ($Na^+$ / $K^+$ ATPases) force the movement of $Na^+$ from the cytoplasm, into the extracellular fluid; and force the movement of $K^+$ from the extracellular fluid, into the cytoplasm. See Figure 7.4.
  - $Na^+$ / $K^+$ pumps are ubiquitous, especially are found in muscle cells, in nerve cells, and in epithelial cells.

## Cotransporters

As described in Chapter 5, cell membranes contain co- and counter-transporters, which use the concentration gradient of one ion (commonly $Na^+$ or $K^+$) to cause conformational changes and transport of another ion (for example, $Cl^-$).

- The $Na^+/K^+/2Cl^-$ cotransporters move $K^+$ and $Cl^-$ in the same direction as the concentration gradient of $Na^+$
  - $Na^+/K^+/2Cl^-$ cotransporters are found in CNS, especially in <u>immature</u> (developing) neurons, as well as in kidney.
  - The high concentration of $Na^+$ in the extracellular fluid, due to the $Na^+$ / $K^+$ pumps, provides a gradient that moves both $K^+$ and $Cl^-$ from the extracellular fluid into the intracellular fluid.
  - Intracellular [$K^+$] and [$Cl^-$] becomes higher; extracellular [$K^+$] and [$Cl^-$] becomes lower.

- *The $K^+/Cl^-$ cotransporters move $Cl^-$ in the same direction as the concentration gradient of $K^+$
  - $K^+/Cl^-$ cotransporters are found in CNS, especially in <u>mature</u> neurons, as well as in kidney.
  - The high concentration of $K^+$ in the intracellular fluid, due to the $Na^+$ / $K^+$ pumps, provides a gradient that moves $Cl^-$ from the intracellular fluid into the extracellular fluid.
  - Intracellular [$Cl^-$] becomes lower and extracellular [$Cl^-$] becomes higher.

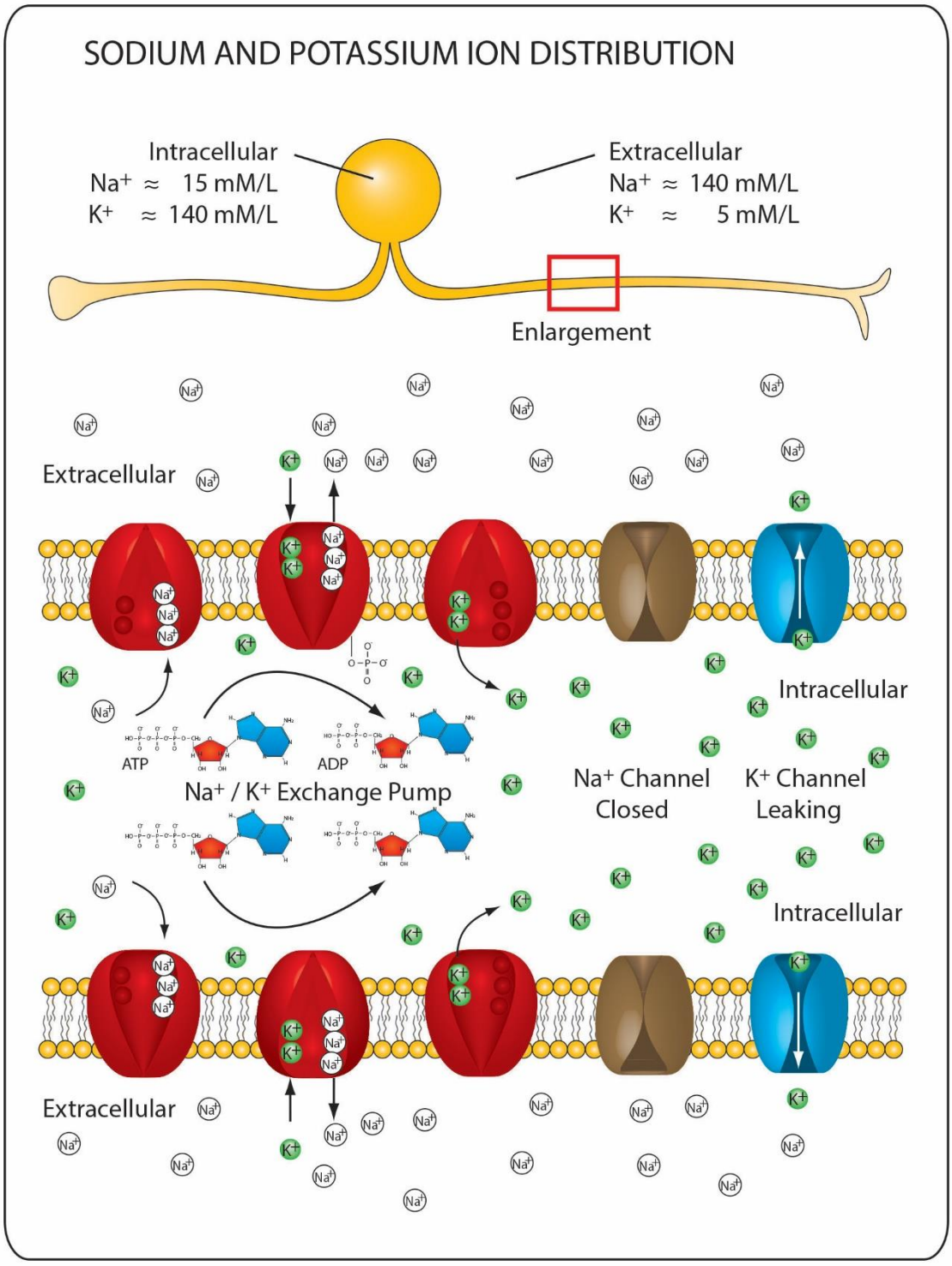


**Figure 7.4 © 2016 David G. Ward, Ph.D.**

## Ion Channels

As described in Chapters 5 and 6, cell membranes contain channels, which are transmembrane proteins that allow ions to pass through membranes from an area of higher concentration to an area of lower concentration. Channels may be passive or gated.

- Passive Channels (Leak Channels) are always open and permit leakage of ions.
  - For example, $K^+$ leak channels and $Cl^-$ leak channels.
- Gated Channels open or close in response to specific stimuli, and include
  - Movement-gated Channels which open or close in response to a mechanical movement, such as touching the skin.
    - For example, movement gated $Na^+$ channels
  - Ligand-gated Channels which open or close in response to binding to specific extracellular chemicals (ligands), especially neurotransmitters.
    - For example, ligand gated $Na^+$, $Ca^{2+}$, and $Cl^-$ channels
  - Voltage-gated Channels which open or close in response to changes in the transmembrane potential.
    - For example, voltage gated $Na^+$, $Ca^{2+}$, and $K^+$ channels

## Resting Membrane Potential

In the resting neuron, an equilibrium (balance) exists between the sodium-potassium pumps and the electrochemical forces caused by the distribution of ions on each side of the cell membrane. This equilibrium is associated with extracellular and intracellular concentrations of sodium, potassium, and chloride as summarized in Table 7.1, below. For completeness, the distribution of calcium, caused by calcium pumps, is also shown.

Table 7.1. Extra-cellular and Intra-cellular concentrations of common Ions

| Ion | Extra-cellular concentration | Intra-cellular concentration |
|---|---|---|
| $Na^+$ | 140 mM/L | 15 mM/L |
| $K^+$ | 5 mM/L | 140 mM/L |
| $Cl^-$ | 115 mM/L (varies) | 10 mM/L (varies) |
| $Ca^{2+}$ | 3 mM/L | 0.0001 mM/L |

The resting membrane potential depends upon the permeability of the cell membrane to the various ions. $K^+$ leak channels are most prominent, making the cell membrane at rest much more permeable to $K^+$ than to $Na^+$. Thus, $K^+$ leaves the cell (from high to low concentration) until the positive charge on the outside pushes the $K^+$ back in.

The equilibrium for the ions involved is quantified by the Goldman equation:

$$Vm^* = 61.5 \times \text{Log} \frac{pK\,[K+]o + pNa\,[Na+]o + pCl\,[Cl-]i}{pK\,[K+]i + pNa\,[Na+]i + pCl\,[Cl-]o}$$

*Vm= membrane potential; p= permeability; o= outside; i= Inside

Using pK = 1, pNa = 0.04, pCl = 0.5, and the concentration data from Table 7.1:

$$-67.88 = 61.5 \times \text{Log} \frac{1\,[5]o + 0.04\,[140]o + 0.5\,[10]i}{1\,[140]i + 0.04\,[15]i + 0.5\,[115]o}$$

In a neuron the resting membrane potential is typically about -65 mV to -70 mV, meaning that the intracellular surface is -65 mV to -70 mV more negative than the extracellular surface. The membrane potential calculated above, -67.88 mV, falls within this range.

# Action Potentials

## Generation of an action potential in a sensory neuron

A sensory stimulus, such as touch, acting on movement gated channels, causes a small change in the membrane potential which is proportional to the stimulus. These small changes in membrane potential are called graded potentials.

The steps in the generation and conduction of an action potential in a sensory neuron are shown and numbered 1-6 in Figure 7.5A. Also see Figure 7.5B.

1) Movement gated sodium channels open, positively charged sodium ions enter the dendrite and a depolarization (positive graded potential) is produced.
2) The positively charged sodium ions spread (diffuse) into the axon; and when a potential of about - 60 mV to - 55 mV (threshold potential) is reached local voltage gated sodium channels open, more sodium ions enter the cytoplasm, and a depolarization is produced. This process causes the local membrane potential to reach about + 30 mV.
3) The local voltage gated sodium channels close.
4) The local voltage gated potassium channels open, positively charged potassium ions leave the cytoplasm, and a repolarization, and often a hyperpolarization is produced. This process causes the local membrane potential to reach about - 70 mV to - 75 mV.
5) The local voltage gated potassium channels close.
6) The positively charged sodium ions spread (diffuse) to more distant areas of the axon and events 2-6 are repeated sequentially from one end of the axon to the other.

Accordingly, an action potential is the name for the changes in membrane potential that result from the sequential opening and closing of the voltage gated $Na^+$ channels and the voltage gated $K^+$ channels, typically from one end of the axon to the other.

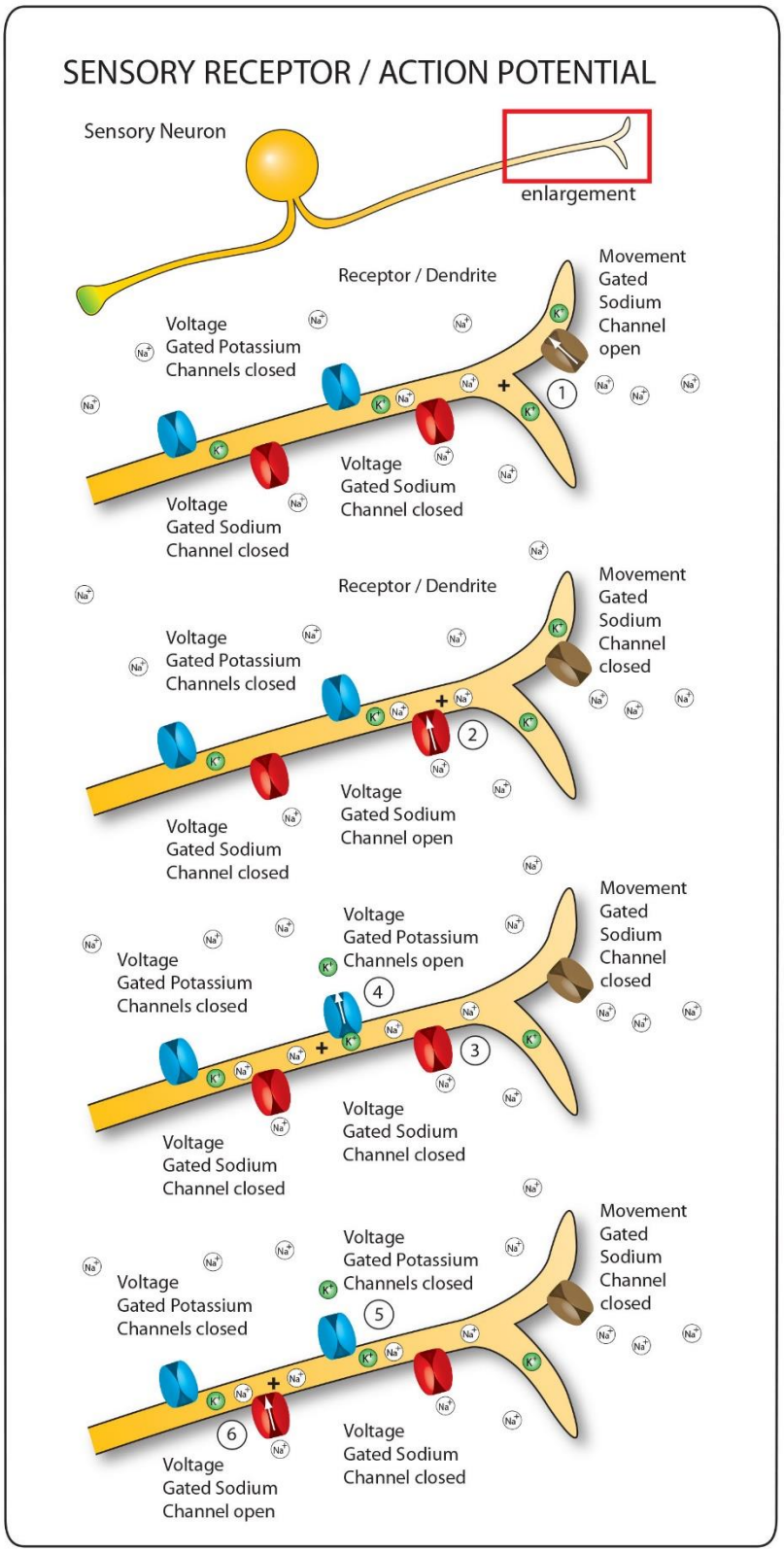


**Figure 7.5A © 2014 David G. Ward, Ph.D.**

A tracing of the changes in the membrane potential as voltage gated $Na^+$ channels and voltage gated $K^+$ channels open and close along the length of an axon is shown in Figure 7.5B. These changes in membrane potential are called the "action potential."

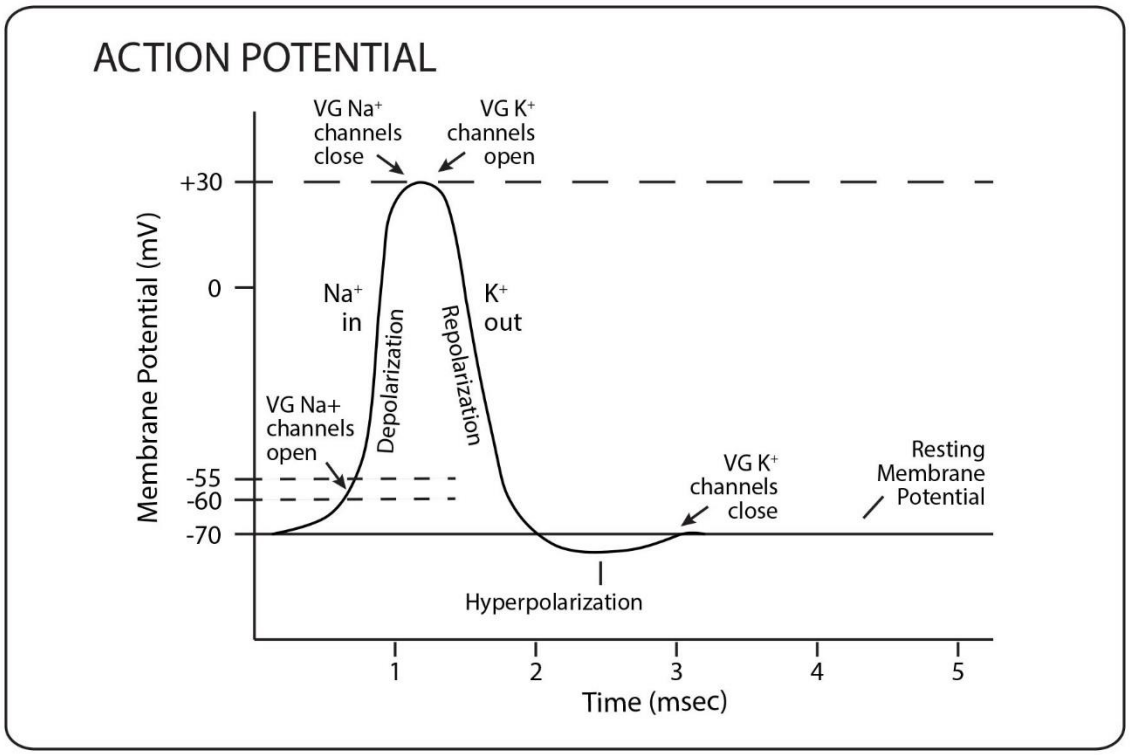


**Figure 7.5B © 2019 David G. Ward, Ph.D.**

There are limits as to how frequently action potentials can occur.

- A new action potential cannot occur at a given location during the time between the sodium channels opening and then closing. This period of time is called the absolute refractory period, and sets a maximum rate (frequency) for the generation and conduction of action potentials.
- After the absolute refractory period, a stronger than normal depolarization (more positive than about -60 mV to -55 mV) can generate another action potential. This period of time is called the relative refractory period.

The speed of conduction of an action potential and frequency of action potentials depends on myelination and axon diameter.

- Myelination restricts movement of ions and allows depolarization of the membrane only at the un-insulated nodes of Ranvier.
- Larger axons allow faster movement of ions through the ion channels of the membrane and permit faster conduction of action potentials.

# Neural (Synaptic) Signaling

## Synaptic Anatomy

Neurons communicate with each other or with muscle by way of synapses, either electrical synapses or chemical synapses.

- Electrical synapses involve gap junctions (ion channels) between adjacent cells, which allow diffusion of ions between the cells
- Chemical synapses involve the release of neurotransmitters. These neurotransmitters diffuse across a synaptic cleft from one neuron to the next neuron or muscle cell. The most common form of neural communication, chemical synapses, is illustrated in Figure 7.6.

    - A neurotransmitter is secreted from the presynaptic membrane of a synaptic bulb into the synaptic cleft.
    - The postsynaptic membrane of a neuron or muscle cell on the opposite side of the synaptic cleft responds to the neurotransmitter.

Synapses may form between cells in several manners.

- Axodendritic synapses form between axons and a dendrite.
- Axosomatic synapses form between axons and a cell body.
- Axoaxonic synapses form between axons and another axon or synaptic bulb.
- Neuromuscular synapses form between axons and a muscle cell.

## Synaptic Neurotransmitter Secretion

The arrival of an action potential at a synaptic bulb of the presynaptic neuron will lead to the release of a neurotransmitter, as illustrated in Figure 7.7.

1) The action potential causes voltage gated sodium channels to open, and the positive charge from the entry of sodium (depolarization) opens voltage gated calcium channels, permitting calcium ions to enter the synaptic bulb from the extracellular fluid.
    - Note: calcium concentration is kept very low in the intracellular fluid by $Ca^{2+}$ pumps ($Ca^{2+}$ ATPase).
2) Calcium stimulates the fusion of the synaptic vesicles with the presynaptic membrane and permits diffusion of the neurotransmitter out of the synaptic vesicle and into the synaptic cleft.

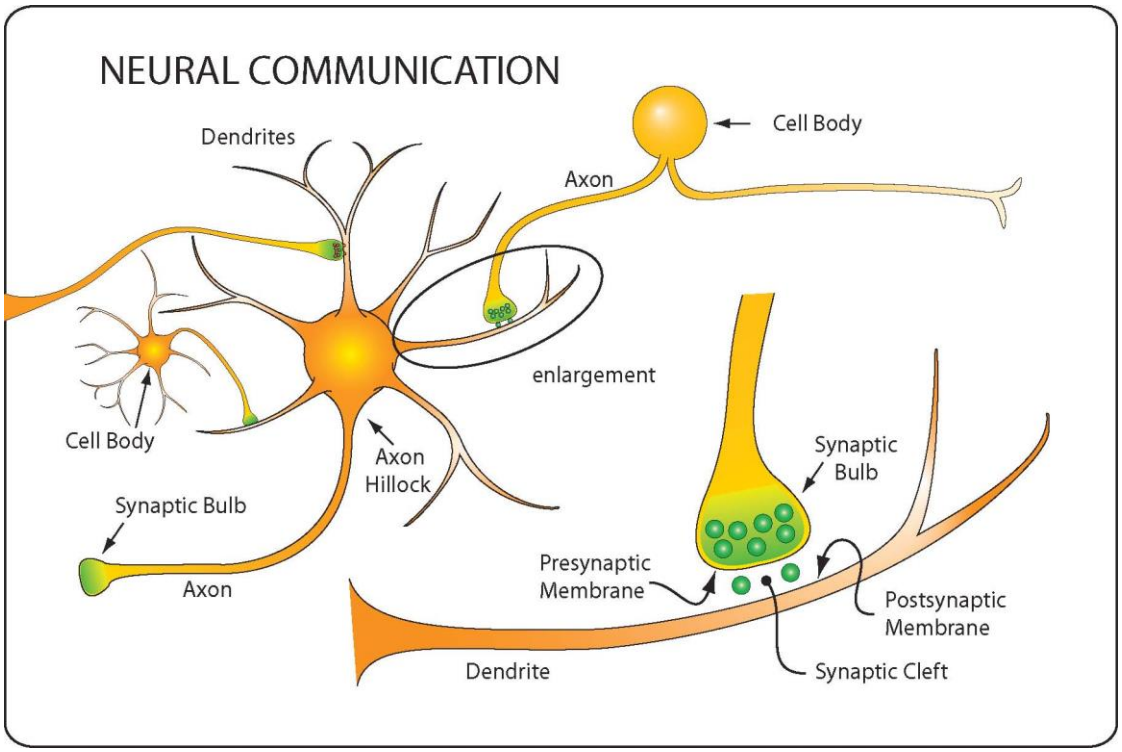


**Figure 7.6 © 2007 David G. Ward, Ph.D.**

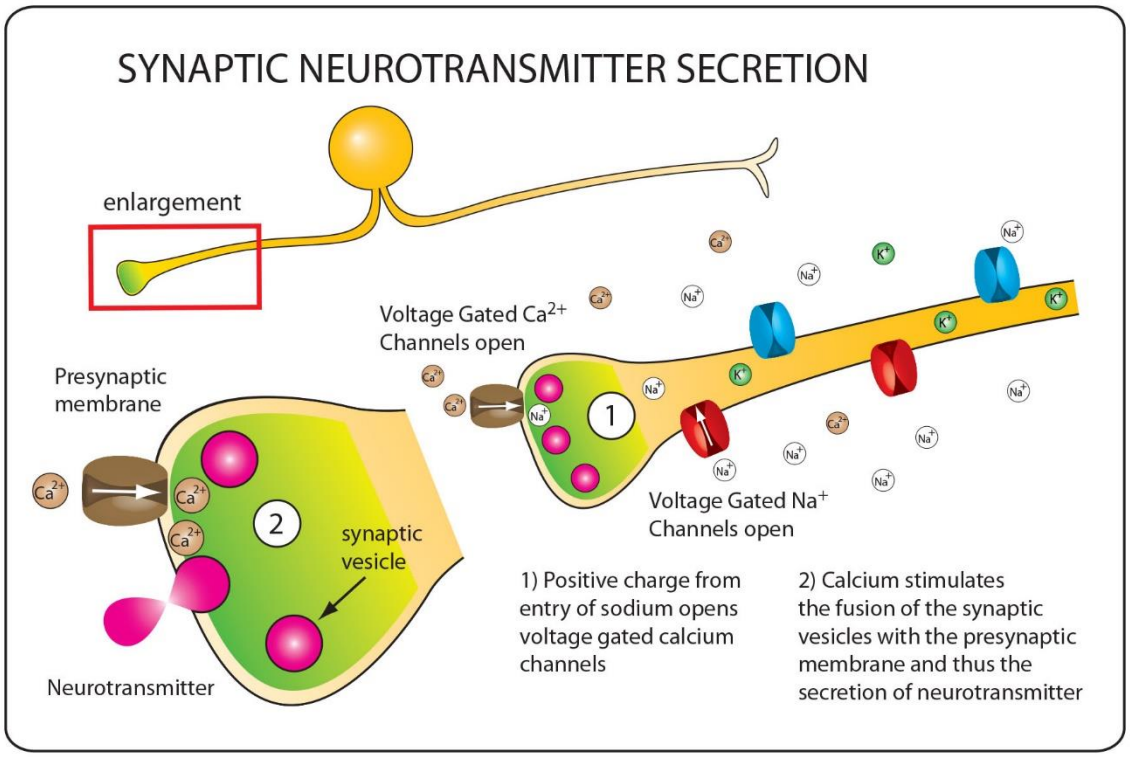


**Figure 7.7 © 2014 David G. Ward, Ph.D.**

The fusion of the synaptic vesicles with the presynaptic membrane and the subsequent release and action of a neurotransmitter are shown in more detail in Figure 7.8.

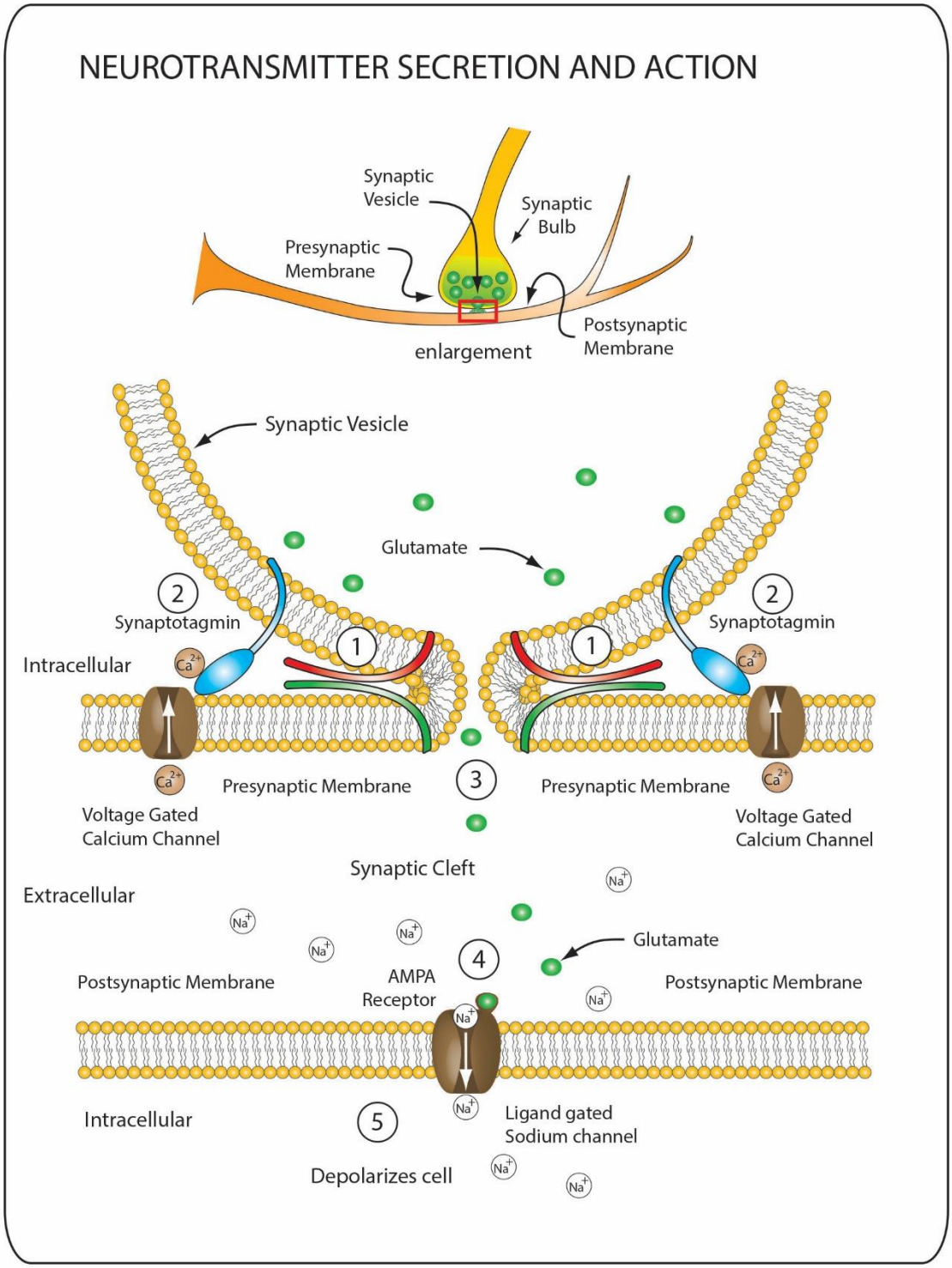


**Figure 7.8 © 2018 David G. Ward, Ph.D.**

1) SNARE-SM proteins (red and green) capture synaptic vesicles and secure (dock, tether) them to the presynaptic membrane.
2) Calcium binds to synaptotagmin(s) (blue), and together with SNARE-SM proteins cause the synaptic vesicles to fuse with the presynaptic membrane and open.
3) The neurotransmitter in the vesicles (glutamate, for example) diffuses into the synaptic cleft.
4) The neurotransmitter binds to receptors on the postsynaptic membrane (ligand gated sodium channels (AMPA receptors, for example)).
5) Ions (sodium, for example) diffuse into the cytoplasm and depolarizes the postsynaptic membrane.

## Action of Neurotransmitters

Neurotransmitters can lead to fast responses or slow responses and these responses can be either excitatory or inhibitory.

- Fast responses involve fast ligand-gated channels (inotropic receptors).
- Slow responses involve G-protein coupled channels (metabotropic receptors).

Figure 7.9 summarizes how opening ligand gated sodium or calcium channels causes excitation (by depolarizing the cell); and how opening ligand gated chloride or potassium channels causes inhibition (by polarizing or hyperpolarizing the cell). The closing of potassium channels can also contribute to excitation.

- **Depolarization** refers to the membrane potential becoming more positive.
- **(Hyper)polarization** refers to the membrane potential becoming more negative.

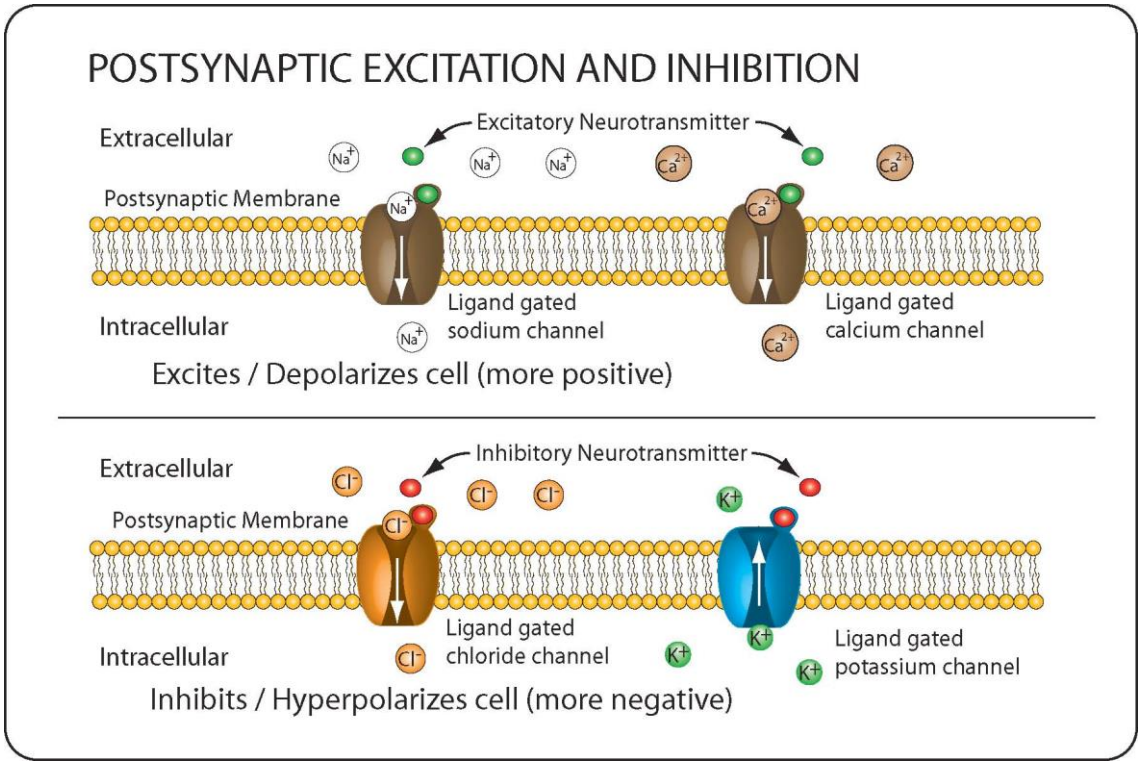


**Figure 7.9 © 2007 David G. Ward, Ph.D.**

Excitatory responses are due to depolarization of the intracellular fluid adjacent to the postsynaptic membrane. These responses are often called **excitatory postsynaptic potentials** (**EPSPs**)

- Fast excitatory postsynaptic potentials (fast EPSPs) are usually caused by the opening of ligand gated sodium or calcium channels. We saw in Chapter 6, Figure 6.3 and in Figure 6.8 how glutamate acting on ligand gated sodium channels (AMPA receptors) allows positively charged sodium ions to enter the cytoplasm, causing depolarization.
- Slow excitatory postsynaptic potentials (slow EPSPs) are often caused by G-protein coupled receptors. The EPSPs lead to the opening of calcium channels and/or the closing of potassium channels. We saw in Figure 6.7 how acetylcholine binds to G-protein coupled receptors (M1/M3 cholinergic) and acts through IP3 and protein kinase C to open calcium channels and to close potassium channels. These processes allow positively charged ions to enter and/or remain in the cytoplasm, causing depolarization.

Inhibitory responses are due to hyperpolarization of the intracellular fluid adjacent to the postsynaptic membrane. These responses are often called **inhibitory postsynaptic potentials** (**IPSPs**)

- Fast inhibitory postsynaptic potentials (fast IPSPs) are usually caused by the opening of chloride channels. We saw in Figure 6.3 how glycine acts on ligand gated chloride channels (e.g. glycine receptors). This process allows negatively charged chloride ions to enter the cell, causing a weak interference with EPSPs or a stronger hyperpolarization (and greater interference with EPSPs.
    - A weak interference with EPSPs occurs in cells that do not transport chloride ions out of their cytoplasm, for example do not use $K^+/Cl^-$ cotransporters.
    - A stronger hyperpolarization (and greater interference with EPSPs) occurs in cells that transport chloride ions out of their cytoplasm, for example do use $K^+/Cl^-$ cotransporters. Refer to **cotransporters** earlier in this chapter.
- Slow inhibitory postsynaptic potentials (slow IPSPs) are usually caused by the opening of G-protein coupled potassium channels. We saw in Figure 6.8 how acetylcholine acts on G-protein coupled receptors (e.g. M2 cholinergic) to open potassium channels. This process allows positively charged potassium ions to leave the cell, causing hyperpolarization.

## Fate of Neurotransmitters

The action of neurotransmitters is usually very brief. After secretion, neurotransmitters may diffuse away, may be transported back into the cell (re-uptake), or may be destroyed by enzymes. The more quickly the neurotransmitter is removed, the shorter the response.

# Neurotransmitters

## Glutamate

Glutamate is the most common excitatory neurotransmitter in the central nervous system, and the most common neurotransmitter secreted by sensory neurons. The action of glutamate on the postsynaptic membrane will depend on the type of receptor. These include AMPA receptors, NMDA receptors, and metabotropic EAA (excitatory amino acid) receptors.

- Glutamate acts on the postsynaptic membrane by binding to **AMPA** (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptors on a specific group of ligand-gated sodium channels, opening them. Sodium ions enter the cell and cause a graded depolarization.
- Glutamate acts on the postsynaptic membrane by binding to specific **NMDA** (*N*-methyl-D-aspartate) receptors on a specific group of ligand-gated calcium channels, opening them. Calcium ions enter the cells and cause a graded depolarization.
    - NMDA receptors are able to bind glutamate only after the cell depolarizes. Thus, neurons with NMDA receptors respond to glutamate only after the neuron is already excited.
    - NMDA receptors are blocked by magnesium at physiological levels. When the cell depolarizes magnesium no longer blocks the NMDA receptor.
- Glutamate acts on the postsynaptic membrane by binding to specific **metabotropic** receptors which are G-protein coupled receptors. Activation of G-protein alpha activates phospholipase C (PLC). Please refer to Figure 6.7 for a description of how PLC catalyzes the conversion of phosphatidylinositol to IP3. This process opens calcium channels, which allows calcium ions to enter the cell causing a graded depolarization.

## Gamma Aminobutyric Acid (GABA) and Glycine

GABA and Glycine are the main inhibitory neurotransmitters in the central nervous system. The action of GABA on the postsynaptic membrane will depend on the type of receptor. These include GABA-A receptors and GABA-B receptors.

- GABA acts on the postsynaptic membrane by binding to **GABA-A** receptors on a specific group of ligand-gated chloride channels, opening them. This process allows chloride ions to enter the cells, causing a graded hyperpolarization
- GABA acts on the postsynaptic membrane by binding to **GABA-B** receptors which are G-protein coupled receptors. Activation of G-protein alpha causes the release of G-protein beta-gamma. Please refer to Figure 6.8, for a description of how G-protein beta-gamma opens potassium channels. This process allows potassium ions to leave the cell, causing a graded hyperpolarization.
- Glycine acts on the postsynaptic membrane by binding to specific **glycine** receptors on a specific group of ligand-gated chloride channels, opening them. This process allows chloride ions to enter the cell, causing a graded hyperpolarization.

## Acetylcholine

Acetylcholine (ACh) is the most common excitatory neurotransmitter in the peripheral nervous system (PNS). ACh is also found in the central nervous system. The action of ACh on the postsynaptic membrane will depend on the type of receptor. These include Nicotinic-m and -n receptors and Muscarinic -1, -2, and -3 receptors. We will come back to this section when we consider skeletal, cardiac and smooth muscle contraction (Chapter 11) and the autonomic nervous system (Chapter 13).

- **Nicotinic-m** (N-m) receptors are found mainly in the motor end plate of skeletal muscle. The organization and excitation of skeletal muscle are considered in Chapter 11. Acetylcholine binds to nicotinic-m receptors, which are ligand-gated sodium channels, opening them. This process allows sodium ions to enter the cell, causing a graded depolarization that will lead to muscle contraction.
- **Nicotinic-n** (N-n) receptors are found mainly on postganglionic neurons in the autonomic portions of the peripheral nervous system. However, some are found in the brain. The structure and functions of the autonomic nervous systems are considered in Chapter 13. Acetylcholine binds to nicotinic-n receptors, which are ligand-gated sodium channels, opening them. This process allows the entry of sodium ions into the cell, causing a graded depolarization.
- **Muscarinic-1** (M-1) receptors are found mainly in neurons, especially in the central nervous system. **Muscarinic-3** (M-3) receptors are found mainly in the sarcolemma of smooth muscle. The organization and excitation of smooth muscle is considered in Chapter 11. Acetylcholine binds to M-1 or M-3 receptors which are G-protein coupled receptors. Phosphorylation of G-protein alpha activates phospholipase C (PLC). Please refer to Figure 6.7, for a description of how PLC catalyzes the conversion of phosphatidylinositol to IP3. This process opens calcium channels, which allows entry of calcium ions into the cytoplasm, causing a graded depolarization and/or muscle contraction. PLC also catalyzes the conversion of phosphatidylinositol to DAG, which activates protein kinase C, which itself closes potassium channels. This latter process prevents potassium from leaking out of the cell, causing an added depolarization.
- **Muscarinic-2** (M-2) receptors are found mainly in neurons in the central nervous system and in the pacemakers of the heart. The heart is considered in Chapter 16. Acetylcholine binds to M-2 receptors which are G-protein coupled receptors. Phosphorylation of G-protein alpha causes the release of G-protein beta-gamma. Please refer to Figure 6.8, for a description of how G-protein beta-gamma opens potassium channels. This process allows potassium ions to leave the cell, causing a graded hyperpolarization.

Acetylcholine has a very short half-life. Immediately after secretion, acetylcholinesterase hydrolyzes the ACh and permits only a passing effect on the postsynaptic membrane.

## Norepinephrine

Norepinephrine is the post-ganglionic neurotransmitter of the Sympathetic nervous system. Norepinephrine is also found in the central nervous system. The action of norepinephrine on the postsynaptic membrane will depend on the type of receptor. These include alpha-1 and -2 receptors and beta-1, -2, and -3 receptors. We will come back to this section when we consider cardiac and smooth muscle contraction (Chapter 11) and the autonomic nervous system (Chapter 13).

- **Alpha-1** receptors are found mainly in the motor end plates of smooth muscle. The action of norepinephrine on alpha-1 receptors is very similar to the action of acetylcholine on muscarinic-3 receptors. Norepinephrine binds to alpha-1 receptors which are G-protein coupled receptors. Phosphorylation of G-protein alpha activates phospholipase C (PLC). Please refer to Figure 6.7, for a description of how PLC catalyzes the conversion of phosphatidylinositol to IP3. This process opens calcium channels, which allows entry of calcium ions into the cytoplasm, causing a graded depolarization and/or muscle contraction. PLC also catalyzes the conversion of phosphatidylinositol to DAG, which activates protein kinase C, which itself closes potassium channels. This latter process prevents potassium from leaking out of the cell, causing an added depolarization.
- **Alpha-2** receptors are found mainly in synaptic bulbs and in the motor end plates of smooth muscle. Norepinephrine binds to alpha-2 receptors which are G-protein coupled receptors. Phosphorylation of G-protein alpha inhibits adenylyl cyclase. Without active adenylyl cyclase and the conversion of ATP to cyclic-AMP, sodium and calcium ion channels are not opened. This process prevents sodium and calcium ions from entering the cell, causing hyperpolarization.
- **Beta-1** receptors are found mainly in cardiac muscle. Norepinephrine binds to beta-1 receptors which are G-protein coupled receptors. Phosphorylation of G-protein alpha activates adenylyl cyclase that catalyzes the conversion of ATP to cyclic-AMP that in turn activates protein kinase A, which opens sodium and calcium ion channels. This process allows sodium and calcium ions to enter the cell, causing depolarization and muscle contraction
- **Beta-2** receptors are found mainly in smooth muscle. Norepinephrine binds to beta-2 receptors which are G-protein coupled receptors. Phosphorylation of G-protein alpha activates adenylyl cyclase. Please refer to Chapter 6 for a description of how adenylyl cyclase catalyzes the conversion of ATP to cyclic-AMP, which activates protein kinase A, which in turn phosphorylates several proteins. Here, these proteins include pumps that move calcium ions out of the intracellular fluid into the sarcoplasmic reticulum; proteins that inhibit the action of phospholipase C; and proteins that inhibit myosin kinase. The role of myosin kinase in the contraction of smooth muscle is considered in Chapter 11.
- **Beta-3** receptors are found mainly in adipose tissue. Norepinephrine binds to beta-3 receptors which are G-protein coupled receptors. Phosphorylation of G-protein alpha activates adenylyl cyclase that catalyzes the conversion of ATP to cyclic-AMP that in turn activates protein kinase A, which phosphorylates and activates enzymes that break down stored lipids (lipolysis).

Norepinephrine has a very short half-life. Immediately after secretion, norepinephrine is transported back into the synaptic bulb by a $Na^+$/norepinephrine co-transporter. (Methamphetamine and cocaine block the transport of norepinephrine back into the synaptic bulb.). Norepinephrine can be broken down inside the cell by monoamine oxidase (MAO) or by catechol-O-methyl transferase (COMT).

### Serotonin

Serotonin is a neurotransmitter found in the GI tract, in blood and in the central nervous system. The action of serotonin on the postsynaptic membrane will depend on the type of receptor. There is one serotonin receptor that is a ligand-gated ion channel. There are at least 12 distinct serotonin receptors that are G-protein coupled. Functions range from controlling GI contraction, and stimulating the clumping of platelets, to stabilizing mood, reducing anxiety, and reducing pain perception.

# Synaptic Integration

### Postsynaptic Potentials

As we have just seen, neurons may secrete excitatory neurotransmitters or inhibitory neurotransmitters. Neurons that secrete excitatory neurotransmitters are often called excitatory neurons, and neurons that secrete inhibitory neurotransmitters are called inhibitory neurons.

- Excitatory neurotransmitters cause excitatory postsynaptic potentials (**EPSPs**) usually by opening sodium or calcium channels or by closing potassium channels, causing depolarization of the postsynaptic membrane.
- Inhibitory neurotransmitters cause inhibitory postsynaptic potentials (**IPSPs**) usually by opening potassium or chloride channels, causing polarization or hyperpolarization of the intracellular fluid adjacent to the postsynaptic membrane.

As shown in Figure 7.10, neurons receive signals from excitatory neurons and from inhibitory neurons. A primary function of neurons is to "listen" to various signals, to integrate the signals and to make some sort of final response based on the assimilation of the signals. The response ends with the neuron generating an action potential or not generating an action potential. The sum of the ionic charges at the axon hillock determines whether an action potential will occur.

Most synapses are formed between axons (synaptic bulbs) and dendrites or soma.

- Dendrites commonly contain ligand gated channels that are responsible for most EPSPs and IPSPs that affect the intracellular fluid adjacent to the postsynaptic membrane.
- Although dendrites are known to contain voltage gated (VG) channels that can elicit dendritic spikes, dendrites rarely are capable of generating action potentials that can propagate out of the dendrites.
- Dendritic spikes may accentuate the effects of EPSPs and IPSPs

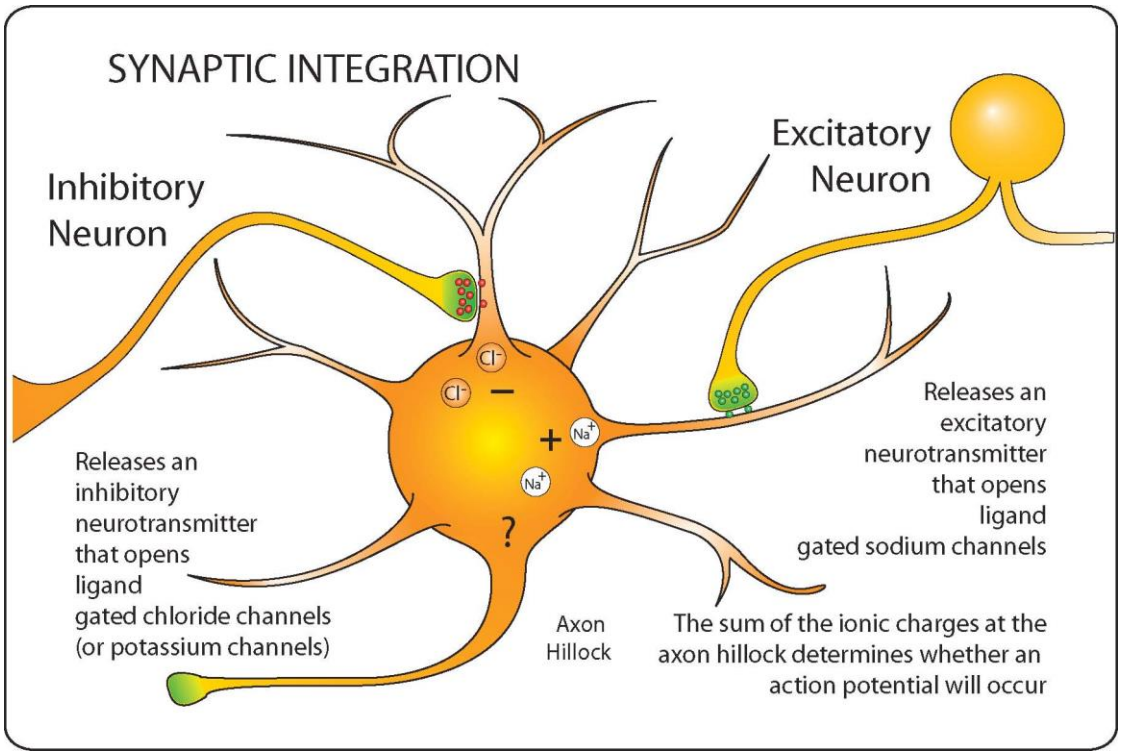


**Figure 7.10 © 2007 David G. Ward, Ph.D.**

However, if the sum of the ionic charges that diffuse to the axon hillock is sufficiently positive, voltage gated sodium channels open and an action potential is produced. In the axon the critical positive charge for opening voltage gated sodium channels is called the **threshold potential**. Figure 7.11 illustrates the generation of an action potential starting at the axon hillock. Notice that the generation of the action potential in the axon hillock uses the same processes as in the sensory neuron shown in Figure 7.5A.

- The axon hillock and axon contain conventional voltage gated (VG) channels.

  1) If the sum of the ionic charges that diffuse to the axon hillock is sufficiently positive, voltage gated (VG) sodium channels in the axon hillock open.
  2) Sodium diffuses into the axon hillock, the membrane potential of the axon hillock reaches about +30mV, and the VG sodium channels in the axon hillock close.
  3) Sodium diffuses into the axon and opens <u>local</u> VG sodium channels in the axon.
  4) The positive charge in the axon closes local VG gated sodium channels in the axon and opens local VG potassium channels in the axon. Potassium diffuses out of the axon, the <u>local</u> membrane potential initially dips to -75mV, the voltage gated (VG) potassium channels close, and the <u>local</u> membrane potential returns to its resting level (-70 mV)

5) The entry of sodium into the axon, and the forward diffusion of sodium, together with the sequential opening and closing sodium and potassium channels, repeats along the length of the axon. This is responsible for action potential.

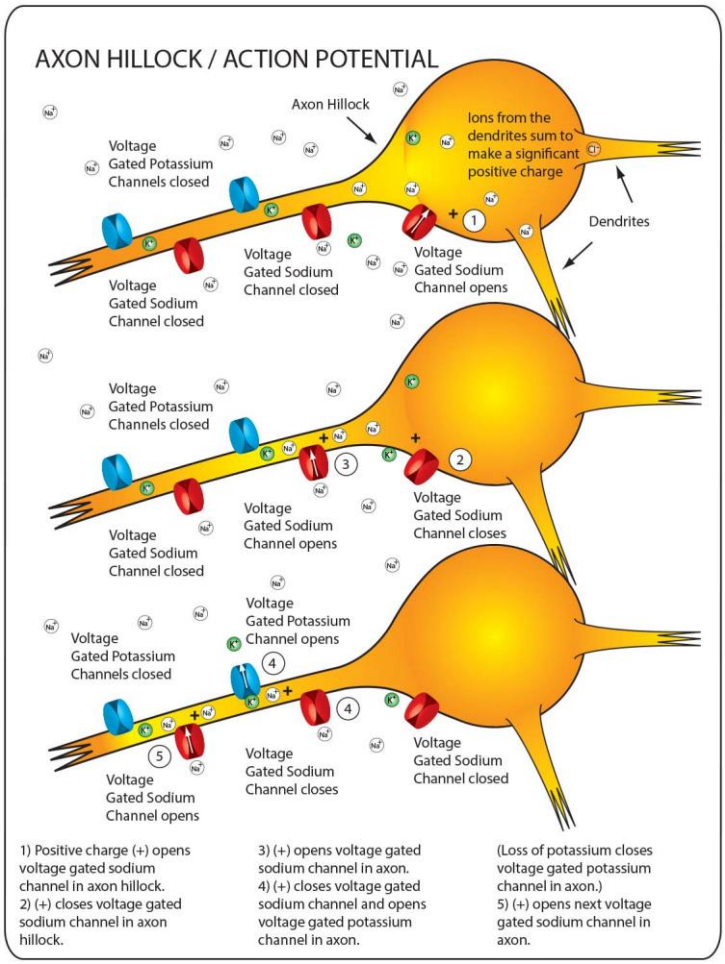


**Figure 7.11 © 2020 David G. Ward, Ph.D.**

## Summation of Postsynaptic Potentials

An action potential is produced only when the sum of the ionic charges generated in the dendrites leads to a significant positive charge in the axon hillock. Summation can occur following the repeated release of neurotransmitters over time, by the release of neurotransmitters at multiple synapses, or by a combination of both.

- The change in membrane potential caused by the accumulation of ions due to the repeated release of neurotransmitters over time is called **temporal summation**.
- The change in membrane potential caused by the accumulation of ions due to the release of neurotransmitters at multiple synapses is called **spatial summation**.

# *Quiz Yourself*

1-5. Matching

| | | | |
|---|---|---|---|
| A) | 140 mM | intracellular concentration of sodium | 1) _____ |
| B) | 105 mM | extracellular concentration of sodium | 2) _____ |
| C) | 15 mM | extracellular concentration of calcium | 3) _____ |
| D) | 5 mM | intracellular concentration of potassium | 4) _____ |
| E) | 3 mM | extracellular concentration of potassium | 5) _____ |

6-10. Matching

| | | | |
|---|---|---|---|
| A) | voltage gated channels | are commonly found in axons | 6) _____ |
| B) | ligand gated channels | are commonly found in dendrites | 7) _____ |
| | | are commonly found in cell bodies | 8) _____ |
| | | are commonly found in presynaptic membranes | 9) _____ |
| | | are commonly found in postsynaptic membranes | 10) _____ |

11-15. Place the following events in the order leading to the release of a neurotransmitter.

| | | |
|---|---|---|
| A) | The neurotransmitter diffuses out of the vesicle into the synaptic cleft | 11) _____ |
| B) | Synaptic vesicle fuse with the presynaptic membrane | 12) _____ |
| C) | An action potential reaches the synaptic bulb | 13) _____ |
| D) | Voltage gated calcium channels open | 14) _____ |
| E) | Calcium enters the intracellular fluid | 15) _____ |

16-20. Matching

| | | | |
|---|---|---|---|
| A) | Slow EPSP | caused by opening ligand gated sodium channels | 16) _____ |
| B) | Fast EPSP | caused by opening ligand gated chloride channels | 17) _____ |
| C) | Slow IPSP | caused by opening calcium channels that are G-protein coupled | 18) _____ |
| D) | Fast IPSP | caused by closing potassium channels that are G-protein coupled | 19) _____ |
| | | caused by opening potassium channels that are G-protein coupled | 20) _____ |

Fill in

21. Neurotransmitters are released from _____ _____.

22. _____ is essential for the fusion of the synaptic vesicles to the presynaptic membrane.

23. Rapid release of neurotransmitter at a single synapse can cause _____ summation.

24. _____ gated channels open or close in response to specific chemicals.

25. Neurotransmitters are _____ soluble.

Study Questions

1. Describe the general organization and purpose of unipolar and multipolar neurons.
2. Describe the intracellular and extracellular distribution of common ions and explain their role in the generation of the resting membrane potential.
3. Explain the role of membrane potentials and ion channels in the generation and conduction of action potentials.
4. Explain the function of synaptic communication and explain the mechanisms responsible for the secretion of neurotransmitters.
5. Explain how postsynaptic receptors respond to common neurotransmitters, and the significance of EPSPs and IPSPs.